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EXERTIONAL HEATSTROKE IN SOLDIERS: AN ANALYSIS OF PREDISPOSING FACTORS, RECOVERY RATES, AND RESIDUAL HEAT INTOLERANCE

US ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts

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UNITED STATES ARMY
MEDICAL RESEARCH & DEVELOPMENT COMMAND

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Ten prior heatstroke patients (PH) were observed in our laboratory during a two-week protocol which measured heat acclimation ability, heat tolerance responses, fluid-electrolyte balance, thermoregulation, and blood values. Nine PH exhibited normal heat acclimation adaptations ~~(40.1°C, 7 d, 90 min·d^{-1})~~, i.e. thermoregulation, sweat gland function, whole-body sodium and potassium balance, and clinical values ~~at 61±~~ 7 d after exertional heatstroke. One PH (subject A) did not adapt to exercise in the heat and was defined as heat intolerant, but in a later trial (11.5 months post-heatstroke) manifested heat tolerance by virtue of successful heat acclimation. However, when evaluated by a six-hour heat tolerance test, two PH (subjects A and D) were defined heat intolerant. It was concluded that: (1) sleep loss and generalized fatigue were the most common predisposing factors for PH; (2) recovery from exertional heatstroke was idiosyncratic and may require up to one year; (3) no PH were hereditarily heat intolerant, prior to exertional heatstroke; (4) no measured variable predicted recovery from exertional

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19. heatstroke, or heat acclimation responses; (5) heat intolerance occurs in a small percentage of prior heatstroke patients, and may be transient or prolonged.

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TECHNICAL REPORT NO. T5-90

Exertional Heatstroke In Soldiers: An Analysis of Predisposing Factors, Recovery Rates, and Residual Heat Intolerance

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Abstract

Ten prior heatstroke patients (PH) were observed in our laboratory during a two-week protocol which measured heat acclimation ability, heat tolerance responses, fluid-electrolyte balance, thermoregulation, and blood values. Nine PH exhibited normal heat acclimation adaptations (40.1°C, 7 d, 90 $min \cdot d^{-1}$): i.e thermoregulation, sweat gland function, whole-body sodium and potassium balance, and clinical values at 61 $\pm$ 7 d after exertional heatstroke. One PH (subject A) did not adapt to exercise in the heat and was defined as heat intolerant, but in a later trial (11.5 months post-heatstroke) manifested heat tolerance by virtue of successful heat acclimation. However, when evaluated by a six-hour heat tolerance test, two PH (subjects A and D) were defined heat intolerant. It was concluded that: (1) sleep loss and generalized fatigue were the most common predisposing factors for PH; (2) recovery from exertional heatstroke was idiosyncratic and may require up to one year; (3) no PH were hereditarily heat intolerant, prior to exertional heatstroke; (4) no measured variable predicted recovery from exertional heatstroke, or heat acclimation responses; (5) heat intolerance occurs in a small percentage of prior heatstroke patients, and may be transient or prolonged.

Introduction

Evaluating the ability of recovering prior heatstroke patients to exercise in a hot environment is a difficult process for attending physicians. When prior heatstroke patients are determined to be "clinically normal", they still may be heat intolerant. This can occur because the extent of the multiple tissue/organ injury of heatstroke and the rate of recovery from heatstroke are highly individualized. This individualized rate of recovery is largely due to the variabilty inherent in each episode (i.e. onset, duration, and intensity of hyperthermia) and to intra-subject variability. Keren et al. (25), for example, observed that the heat intolerance of one male, who experienced heatstroke twice, was temporary and was resolved five months after the second heatstroke episode. Bianchi et al. (8) found a variety of histological abnormalities in the liver tissue of two distance runners, which were resolved 11 - 12 months after heatstroke occurred. However, other laboratory trials (16,43) have demonstrated that some prior heatstroke patients were heat intolerant 2 - 5 years after they experienced heatstroke.

Heat intolerance has been defined (16,38,45) as an inability to adapt to exercise in a hot environment, suggesting that classical heat acclimation adaptations (e.g. reductions in heart rate, rectal temperature) do not occur in prior heatstroke patients who are heat intolerant. Heat acclimation in healthy humans ordinarily requires 7 - 10 days and results in improved ability to exercise and live in the heat (46). However, the

nature and extent of the physiological adaptations of heat intolerant prior heatstroke patients, heat tolerant prior heatstroke patients, and normal individuals have not been clearly described. Although many case reports exist (5,7,14,25,36,44,50), only three previous controlled laboratory investigations (16,40,43) have utilized prior heatstroke patients. However, none of compared of fluid-electrolyte, cardiovascular, or thermoregulatory responses of prior heatstroke patients versus control subjects, during heat acclimation trials. Thus, this technical report focuses on the evaluation of 10 prior exertional heatstroke patients in our laboratory. The time elapsed between the exertional heatstroke episode and laboratory testing (mean $\pm$ SE: 61 $\pm$ 7 d) was a unique feature of this investigation, since other laboratory studies (16,40,43) evaluated prior heatstroke patients 2 - 5 years after they had experienced heatstroke.

Military Relevance

The findings of the current investigation may provide additional guidance for U.S. Army medical officers regarding the fitness of prior heatstroke patients to return to duty. Currently, TB MED 507 (July 1980) notes that increased susceptibilty to heat injury may persist from a few weeks to an indefinite period of time.

> "It is important to emphasize that the heat regulating centers may be extremely labile for many weeks after an attack... An alternative view is that the individual is a member of a susceptible

population and remains susceptible.

It is recognized that some individuals are heat intolerant after experiencing heatstroke, while others exhibit normal heat tolerance (36); however, the reasons for these differential responses are not understood.

Cooperation between the MEDDAC, Martin Army Community Hospital, Fort Benning, GA and USARIEM allowed the identification and analysis of predisposing factors, recovery rates, and residual heat intolerance in ten prior heatstroke patients. The development of a data base consisting of observations on PH provides a better understanding of the mechanism of heat intolerance in prior heatstroke patients, prognosis, and time course of recovery from exertional heatstroke. An improved understanding of recovery from heatstroke also could assist commanders and training instructors, who are responsible for prevention of heat injury to those prior heatstroke patients who may be predisposed to further heat injury. The heat-injured soldier also may benefit from such a data base because a decision to medically board that soldier is likely to be a career-ending decision; an accurate assessment of his/her heat tolerance status would clearly be beneficial. Finally, the U.S. Army may benefit from such a data base. Following heatstroke, soldiers may be: (a) assigned to medical holding companies for lengthy periods; (b) placed on restricted physical training and heat exposure schedules of variable length; (c) medically boarded and released from active duty because they are no longer considered to be

"worldwide deployable"; or (d) returned to their unit for duty. Options a, b, and c represent loss of normal duty time. If clinical/laboratory factors (or heat tolerance tests) were identified/designed which allowed prediction of heat intolerance among prior heatstroke patients, these could prevent great losses of training, experience, time, and money for the U.S. Army.

Purposes

The purposes of this investigation were to describe in prior heatstroke patients the time course and nature of recovery from exertional heatstroke, their ability to acclimate to heat (daily 90 min exposure), their heat tolerance during a six-hour exercise-heat exposure, and to identify the host or situational factors which may have predisposed PH to heatstroke.

Terminology

The eight terms and abbreviations which follow are defined for ease of understanding:

PH - specifically, the 10 male prior heatstroke patients who participated in this investigation

P1, P2 - two subgroups of PH (n = 10), created for the purpose of serum enzyme data analysis. Group P1 (n = 7) exhibited normal serum enzymes during this investigation, whereas group P2 (n = 3) exhibited elevated serum enzymes (see Results).

HTT_{pre} - six-hour test which occurred before the initial heat acclimation trial (day 1)

HTT_{post} - six-hour test which occurred after the final heat acclimation trial (day 9)

CLINICALLY NORMAL - absence of symptoms, no abnormal laboratory values

HEAT INTOLERANCE - (a) the inability to adapt to exercise in the heat (16,38,45), or (b) failure to perform adequately on a heat tolerance test (16,40,43). The former definition utilizes longitudinal observations during repeated days of heat acclimation, while the latter definition utilizes physiological limits or predetermined standards, during a single, exercise-oriented heat tolerance test. Single heat tolerance tests (definition b above) are convenient and conducive to mass screening, and were originally designed to simulate 6 - 8 h of shift work. It is important to recognize that these two forms of evaluating heat intolerance may measure different aspects of heat tolerance.

HEAT ACCLIMATIZATION - an improved ability to live and work in a hot environment, classically identified by reductions in heart rate and rectal temperature.

HEAT ACCLIMATION - heat acclimatization which involves recurrent exercise in an artificial environment (i.e. climatic chamber)

Methods

This investigation was approved by the USARIEM institutional review board, and informed, written consent was obtained from all subjects, in accordance with AR 70-25. Ten male PH participated

in this study. PH were declared clinically normal by their attending physicians, completed a treadmill exercise stress test with no electrocardiographic abnormalities, and arrived at this laboratory 61 $\pm$ 7 d after exertional heatstroke; all PH were military personnel (4 officers, 6 enlisted). Medical records were obtained from the attending physicians. The criteria used to verify exertional heatstroke were similar to those which we have published earlier (21): rectal temperature $\geq$ 40°C, altered mental status, and elevated serum creatinine phosphokinase (CPK), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Each PH completed a Predisposing Factors Questionnaire prior to testing, to identify factors which may have influenced their health and performance during the five days prior to heatstroke.

The physical characteristics of PH are presented in Table 1. Two PH (subjects A and G) had previously experienced heat exhaustion, but none had a history of heatstroke, childhood febrile seizures, or malignant hyperthermia. PH lived in both temperate and hot climates, prior to experiencing heatstroke. All mean physical characteristics of PH (Table 1), except body fat %, were slightly above the mean of 1170 male soldiers described by De Luca et al. (12), and all fell within $\pm$ 1 standard deviation of the mean. A group of five healthy males served as a control (C) population, and undertook the same protocol (Fig. 1). The mean ($\pm$ SE) characteristics of C were as follows: age - 25 $\pm$ 4 y (range: 18 - 42 y), height - 177 $\pm$ 4 cm,

TABLE 1. Selected characteristics of PH.

	Age (yr)	Height (cm)	Body mass (kg)	Surface area (m^2)	M/SA ($kg \cdot m^{-2}$)	Body fat (%)	$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	Number of Days Post-heatstroke (Initial Testing)
A	44	175	82.420	1.98	41.6	22.4	43.74	56
B	22	182	84.470	2.06	41.0	19.5	53.09	46
C	21	189	79.060	2.06	38.4	10.0	59.85	25
D	24	188	96.010	2.23	43.1	17.9	38.37	69
E	22	168	88.140	1.98	44.5	24.6	45.73	82
F	24	193	97.230	2.22	43.8	18.6	47.31	40
G	26	188	93.580	2.20	42.5	16.8	51.92	48
H	26	175	68.680	1.83	37.5	14.6	58.14	76
I	26	176	85.750	2.02	42.4	17.3	50.59	99
J	24	167	78.890	1.88	42.0	14.3	50.56	67
mean	26	180	85.420	2.05	41.7	17.6	49.93	61
± SE	2	3	2.790	.04	0.7	1.3	2.05	7

EVENT	DAY OF INVESTIGATION										
	B	1	2	3	4	5	6	7	8	9	10
90 min acclimation trial			X	X	X	X	X	X	X		
Six-hour trial		X								X	
Anthropometric indices	X										
Entering body mass	X	X	X	X	X	X	X	X	X	X	
Dietary record	X	X	X	X	X	X	X	X	X	X	
T_{re}, T_{sk}, HR		X	X	X	X	X	X	X	X	X	
Sweat rate		X	X	X	X	X	X	X	X	X	
VO_2 submax		X	X							X	
VO_2 max											X
Blood sample	X	X				X			X	X	
HASG			X								
Whole body washdown			X			X			X		
Urine volume, electrolytes, specific gravity	X	X	X	X	X	X	X	X	X	X	

Figure 1. Schedule of testing and measurements for PII and Control.

body mass - 78.250 ± 7.800 kg, surface area - 2.00 ± 0.09 m^2, mass-to-surface area ratio (M/SA) - 39.7 ± 1.8 $kg \cdot m^{-2}$, body fat % - 14.7 ± 1.9 %, maximal aerobic power (VO_2max) - 52.11 ± 2.37 $ml \cdot kg^{-1} \cdot min^{-1}$. Physical characteristics of PH and C were not statistically different (Table 1). Maximal aerobic power (VO_2max) was measured on day 10 using a progressive, continuous treadmill test conducted at 20°C.

Subject A repeated this protocol (Fig. 1) three times, to assess improvements, if any, in his ability to acclimate to heat; subject F performed three iterations of this protocol, and subjects E and G performed two iterations, in an attempt to monitor progressive reductions in serum CPK values. At the time of heatstroke, five PH were judged to be heat acclimatized, based on subject descriptions of activity and heat exposure. All subjects were unacclimatized at the onset of laboratory testing.

90 MIN HEAT ACCLIMATION TRIALS

Seven days of heat acclimation were used to determine the heat tolerance of PH. All heat acclimation trials were conducted in an environmental chamber maintained at 40.1 ± 2.3°C db, 23.8 ± 1.4°C wb (Fig. 1), and consisted of 90 min of treadmill walking (5.6 $km \cdot h^{-1}$, 5 % grade, 45 ± 2 % of VO_2max) for seven consecutive days. Although day 8 was the end point of heat acclimation, the data for day 7 are reported in Figure 2 because of circumstances beyond the investigators' control on day 8 (i.e. equipment malfunction). Subjects were instructed to drink large quantities of water ad libitum before, during, and after each trial to

insure adequate hydration, and were requested to produce a minimum daily urine volume of 2 l. A trial was terminated if heart rate (HR) exceeded 180 beats·min^{-1}, if rectal temperature (T_{re}) exceeded 39.0°C, or if T_{re} increased $\geq$ 0.6°C during any five min period. HR was recorded continuously using an electrocardiographic telemetry system (Hewlett-Packard). T_{re} was measured via a rectal probe inserted 8 cm beyond the anal sphincter, and mean weighted skin temperature (T_{sk}) was calculated by using a three site derivation. The rate of body heat storage was calculated using the following formula:

$$\text{Heat Storage } (Cal \cdot m^{-2} \cdot h^{-1}) = M \cdot S \cdot MBT \cdot SA^{-1} \qquad \text{(Eq. 1)}$$

where M = body mass (kg)

S = specific heat constant (0.83 $W \cdot h^{-1} \cdot kg^{-1} \cdot °C^{-1}$)

MBT = change in mean body temperature $(0.8 \cdot T_{re} + 0.2 \cdot T_{sk})$

SA = surface area (m^2) (11).

Whole body sweat rate ($l \cdot h^{-1}$) was measured using body weight differences (corrected for water intake and urine output) pre-post trial, and was normalized for surface area ($g \cdot m^{-2} \cdot h^{-1}$). Sweat sensitivity was calculated as a measure of sweat rate per degree rise in T_{re} ($g \cdot m^{-2} \cdot h^{-1} \cdot °C^{-1}$). The number of heat activated sweat glands (HASG) was determined at the end of exercise, by covering an area of skin over the scapula with a layer of vaseline petroleum jelly. Microphotography (35mm) was used to provide a permanent record of the number of active sweat glands (appearing as a bead of sweat) per cm^2. Sweat electrolyte losses during

exercise were measured on days 2, 5, 8 using a previously described whole body washdown technique (1,3). Sweat electrolyte loss (total mEq) was calculated by multiplying the volume of rinse water by the concentration of electrolytes in the rinse water. Sweat electrolyte concentration ($mEq \cdot l^{-1}$) was calculated using total electrolyte loss and whole body sweat rate.

Pre-exercise body weight and urine specific gravity were measured each day at 0730h. Urine volume and electrolyte concentration ($mEq \cdot l^{-1}$) were used to calculate the daily loss of electrolytes in the urine ($mEq \cdot 24\ h^{-1}$). Subjects carried clean, inert urine collection containers during their daily business and returned the containers every 24 h. Sodium (Na^+) and potassium (K^+) intake ($mEq \cdot d^{-1}$) were determined from dietary records which subjects maintained throughout the investigation.

Blood samples were taken from an antecubital vein pre-exercise, after subjects had stood quietly for 20 min in the heat, and post-exercise. The following clinical assays were performed: hematocrit (standard microcapillary technique), hemoglobin (cyanmethemoglobin technique), total protein, osmolality (freezing point depression), and the electrolytes Na^+ and K^+ (flame photometry). Percentage change in plasma volume (PV%) was calculated from pre-exercise hematocrit and hemoglobin values (13). Blood samples were were also analyzed for the following clinically relevant enzymes: CPK, LDH, AST, and ALT. If a subject had enzyme levels above the normal clinical range, he was scheduled for a second iteration of this protocol within 3

- 6 months.

SIX-HOUR HEAT TOLERANCE TESTS

A six-hour trial was performed in the heat (3 h walking, 3 h rest) by all subjects prior to the initial 90 min heat acclimation trial (HTT_{pre}), and on the day following the seventh day of heat acclimation (HTT_{post}). This six-hour trial (3) has been described elsewhere. Briefly stated, exercise bouts consisted of walking on a motorized treadmill for 30 min each h (4.8 $km \cdot h^{-1}$, 5% grade, 14.5 km walked $\cdot$ 6 h^{-1}, 724 m climbed $\cdot$ 6 h^{-1}, 37 $\pm$ 1 $\%VO_2max$), and were followed by 30 min of sitting. Six exercise-rest cycles were conducted each day, under chamber conditions which were the same as those noted above for the 90 min heat acclimation trials. Other methods used during the six-hour trial were identical to those described above for 90 min trials (1).

DATA ANALYSIS

Two-way ANOVA with Newman-Keuls post hoc comparisons were used to identify significant differences between PH and C, and between heat acclimation days or six hour trials. Student's t-test was used to compare descriptive characteristics, training, and $VO_2submax$ between groups. Statistical correlation coefficients were calculated via multiple linear regression analysis.

The data of subject A were eliminated, in the statistical analyses of 90 min HA trials (see results below), because he exhibited heat intolerance. The data of subjects A and D

were eliminated, in the statistical analyses of six-hour trials (see results below). Data for subject B were also eliminated in the statistical analyses of six-hour trials, since he was unable to participate in HTT_{pre}. PH were subdivided into groups P1 and P2, for the sole purpose of enzyme data analysis (see Terminology and Results sections). It should be noted that all subjects underwent a 15 min step test (43) in a temperate environment (25.8°C), two days prior to the start of heat acclimation. The methods of this step test have been published elsewhere (2), and the current results are in review.

Results

Situational factors present at the time of heatstroke are summarized in Table 2. Although dry bulb temperatures were moderate, relative humidity was high in every reported case. Subjects G and H experienced heatstroke during the same training run. Six PH (subjects E through J) were involved in specialized military training (i.e. Airborne school, basic training) which required an abrupt change in lifestyle (e.g. intense physical activity, altered sleep pattern, frequent psychological stress).

Table 3 lists selected characteristics of PH during each heatstroke episode and subsequent hospitalization. The duration of altered mental status was not significantly correlated ($p > .05$) with either the peak serum enzyme levels during hospitalization (Table 3) or the peak serum enzyme levels observed during heat acclimation trials.

TABLE 2. Situational factors present at the time heatstroke occurred.

Subject	Time of day	Ambient conditions *		Exercise factors			Clothing Worn	Undergoing specialized training? **
		db temp. (^{o}C)	Relative humidity (%)	Type of activity	Estimated speed of run ($km \cdot h^{-1}$)	Distance completed (km)		
A	0700	23	--	PT	12.1	4.8	T	NO
B	0600	25	97	PT	12.1	8.9	T	NO
C	1000	23	66	CF	15.3	10.0	T	NO
D	0600	22	98	PT	12.1	7.2	--	NO
E	0600	19	96	PT	12.1	6.4	B	YES
F	0900	28	85	PT	12.1	7.2	B	YES
G	0630	23	86	PT	12.1	4.8	B	YES
H	0630	23	86	PT	12.1	4.8	B	YES
I	0700	19	--	PT	13.8	4.8	B	YES
J	1000	--	--	CF	13.8	8.1	T	YES

Abbreviations: db temp. - dry bulb temperature; PT - group physical training run; CF - competitive footrace; T - wore t-shirt, shorts, socks, sneakers and undershorts; B - wore t-shirt, cotton trousers, socks, sneakers and undershorts.

* - official meterological records

** - involved special military training, such as Basic/Airborne/Ranger Training

Table 3. Characteristics of PH during field observations and hospitalization.

Subject	Maximal T_{re} (°C)*	Spontaneous cooling?	Mental status and duration (h)	Peak post-heatstroke serum enzyme levels ** CPK (units·l^{-1})	LDH (units·l^{-1})	AST (units·l^{-1})	ALT (units·l^{-1})
A	40.0	no	disoriented (---)	18,120 (5)	500 (4)	281 (5)	196 (3)
B	41.1	no	coma (7.5)	---	***	***	---
C	41.1	no	coma (0.4)	263 (1)	294 (1)	351 (3)	221 (5)
D	41.1	no	disoriented (0.3)	327 (2)	821 (2)	4,680 (2)	---
E	41.1	no	disoriented (1.0)	1,703 (1)	405 (1)	149 (2)	148 (2)
F	41.1	---	disoriented (5.0)	1,928 (1)	406 (1)	111 (4)	202 (5)
G	41.1	---	coma (0.4)	3,820 (1)	---	206 (2)	210 (3)
H	41.8	no	coma (---)	7,480 (1)	522 (1)	284 (2)	407 (2)
I	41.1	---	coma (0.1)	3,182 (1)	260 (1)	---	88 (1)
J	40.4	no	disoriented (0.2)	14,160 (2)	1,390 (2)	1,200 (2)	2,145 (3)
mean	41.0			5,664	575	908	452
± SE	±0.2			± 2,133	± 132	± 553	± 294

* - All measurements were taken in the field, except patient J (emergency room). Some rectal thermometers read only to 41.1°C.

** - Number of days to reach maximal level is shown in parentheses. Normal enzyme concentration ranges are: CPK - 33-213 units·l^{-1}, LDH - 92-186 units·l^{-1}, AST - 7-32 units·l^{-1}, ALT - 2-45 units·l^{-1}.

*** - Serum enzyme measurements were made on post-heatstroke day 4 only, as follows: LDH - 865 units·l^{-1}, AST - 490 units·l^{-1}.

Sleep loss, generalized fatigue, a long exercise bout (or many exercise sessions each day), and a single long heat exposure were the most prevalent predisposing factors acknowledged by PH (Table 4).

90 MIN HEAT ACCLIMATION TRIALS

The HR and T_{re} responses of PH and C on day 2 and day 7 are illustrated in Fig. 2. Both PH and C showed significant decreases in HR ($p < .05$) and T_{re} ($p < .025$) by day 7; this indicated that nine PH acclimated normally, and were defined as heat tolerant. The change in final HR and final T_{re} (day 2 versus day 7) for PH during heat acclimation (Fig. 2), as indicators of the degree of HA, were not significantly correlated ($p > .05$) with either the peak serum enzyme levels during hospitalization (Table 3) or the peak serum enzyme levels observed during heat acclimation trials (Fig. 3), as indicators of heatstroke injury.

Subject A was defined as heat intolerant, using the definition of Strydom (45) and others (16,38), since he was unable ($T_{re} > 39°C$) to adapt to exercise during 90 min trials. Data for Subject A were deleted from the PH group and the statistical analyses of heat acclimation trials were performed using n = 9 for PH. Subject A was scheduled for a second and third iteration of this protocol, at seven and 11.5 months following heatstroke, due to his inability to acclimate. He was heat intolerant during the second iteration, but exhibited improved HR and T_{re} adaptations during the third iteration, and

TABLE 4. Results of Predisposing Factors Questionnaire administered at initial meeting with PH.

Predisposing factor or warning signal	Subjects who acknowledged this factor (n = 10)*
sleep loss	B, D, E, F, G, H, J
generalized fatigue	D, E, F, G, H, I
a warning signal of impending illness	B, D, E, F, G, I
a long exercise bout or workout	B, E, F, H, J
a long heat exposure (e.g. mowing grass, physical training)	B, F, G, H, J
a heat wave	B, E, G, H
reduced sweat secretion	B, E, J
fever or disease	B, I, J
dizzy, lightheaded	D, E
dehydration	J
taking medication (i.e. antihistamine)	A
excessive use of alcohol	J
excessive use of caffeine	D
consumption of low salt diet	E
previous heat illness	A
sunburn or skin rash	B
immunization or innoculation	-
use of diuretics	-
previous difficulty with exercise in the heat	-
diarrhea or vomiting	-

* - during the five days prior to heatstroke episode; see Table 1 for subject characteristics

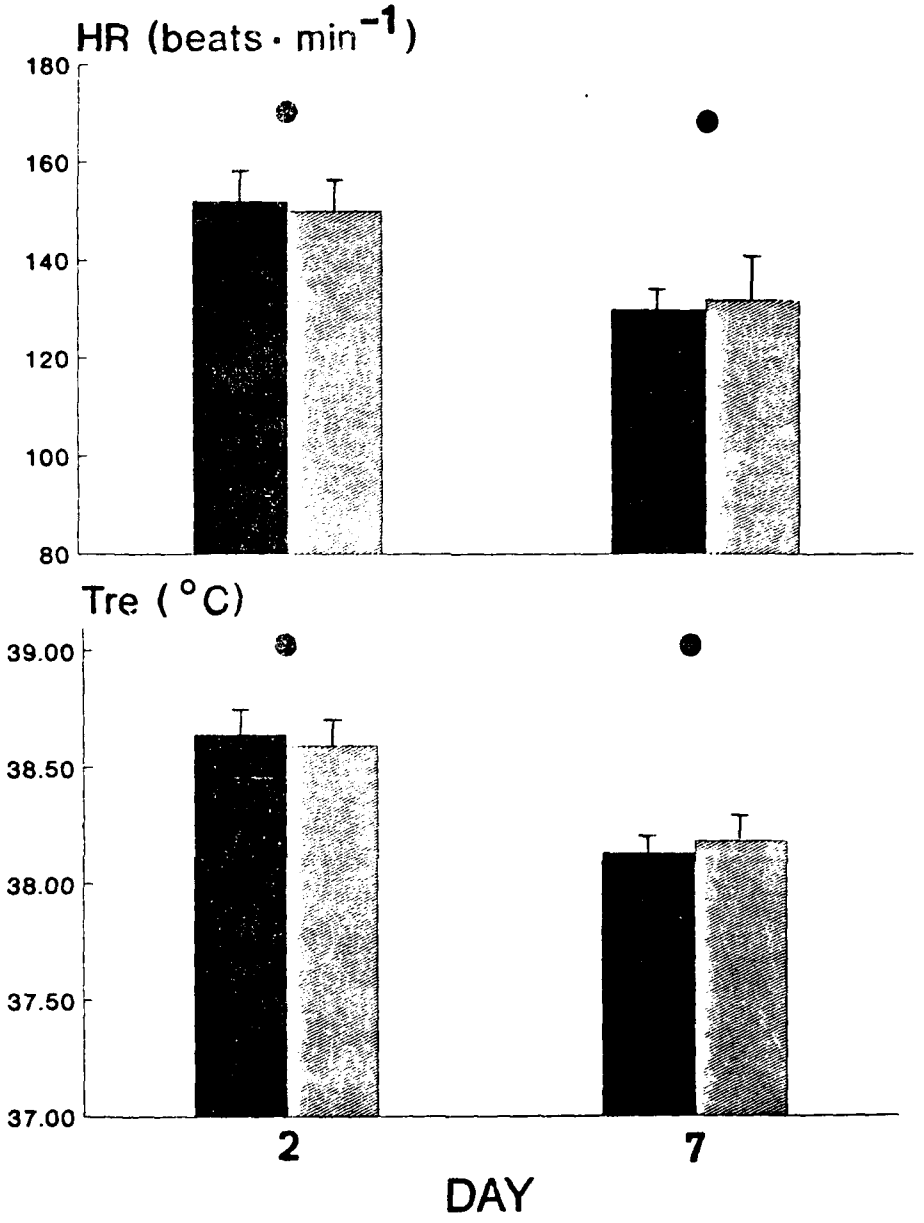

Figure 2. Mean (±SE) final HR and Tre values during heat acclimation, on day 2 and day 7. Symbols: closed circle - heat intolerant subject A, closed bars - PH (n = 9), shaded bars - Control (n = 5). Significant differences ($p<.05$) existed between day 2 and day 7 HR values, for PH and Control. Significant differences existed between day 2 and day 7 Tre values, for PH ($p<.01$) and Control ($p<.025$).

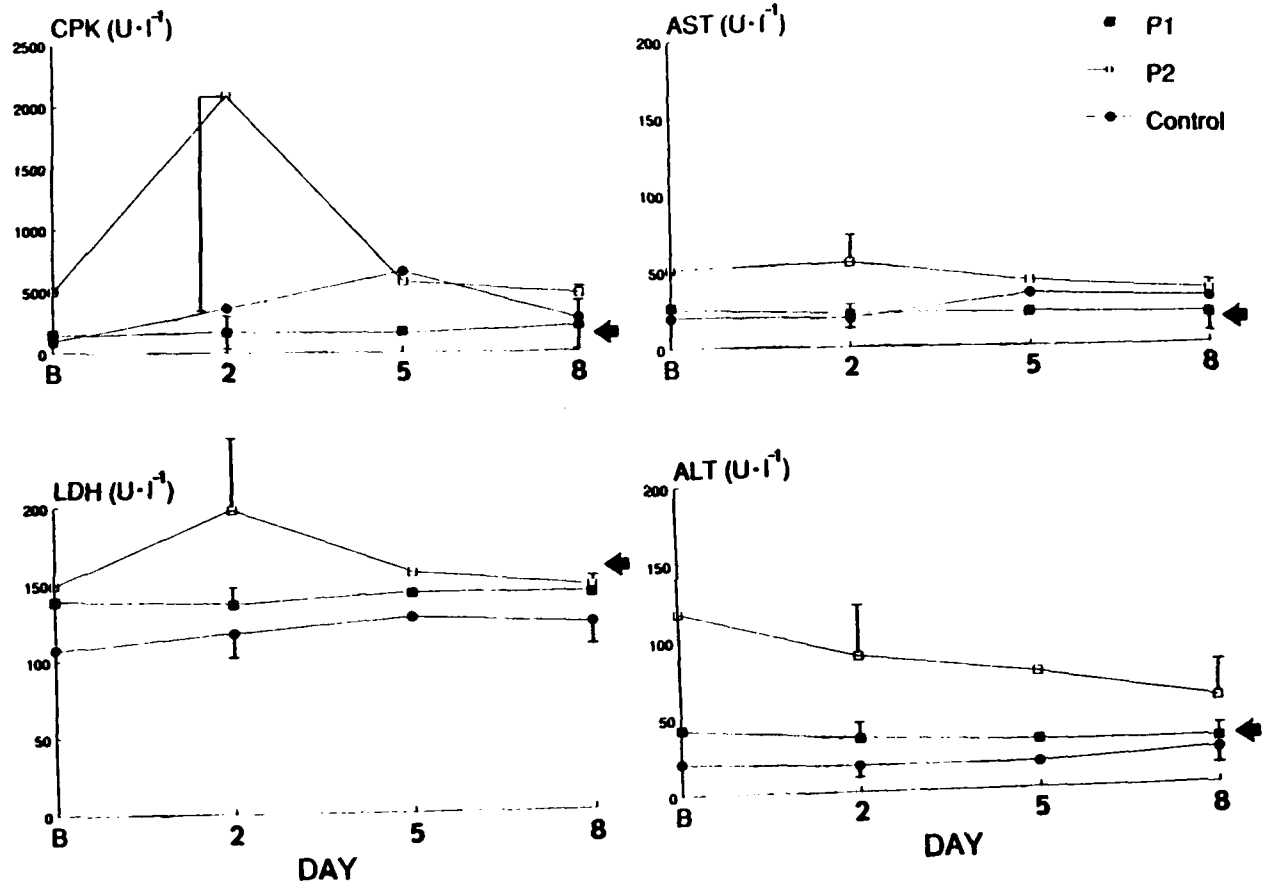

Fig. 3. Pre-exercise serum CPK, LDH, AST, and ALT values (mean ± SE) of groups P1 (n = 7), P2 (n = 3), and Control (n = 5). Group P1 and P2 were subsamples of PH, separated for the purpose of serum enzyme analysis (see results). Arrows denote the upper level of the normal range for each enzyme. Significant differences ($p<.01$) existed between P2 and P1 (day 2), and between P2 and Control (day 2) for CPK, LDH, and AST values. AST values were also significantly different ($p<.01$) between P2 and P1 on B. Significant differences ($p<.05$) existed between P2 and P1 (B, day 2, day 5), and between P2 and Control (B, day 2, day 5) for ALT values.

was defined heat tolerant at that time. The factors which distinguished subject A from other PH and C were: body fat %, age, VO_2max (Table 1), two previous experiences with heat exhaustion, the peak post-heatstroke CPK level (Table 3), and the number of days to reach peak post-heatstroke CPK, ALT and AST levels (Table 3); he exhibited no signs of low-grade viral or bacterial infections.

Thermoregulatory measurements made during 90 min heat acclimation trials, for the nine heat tolerant PH and C indicated no significant between-day differences in the following variables: T_{sk}, heat storage, $T_{re} - T_{sk}$, HASG, sweat rate, and sweat sensitivity. Previous investigations (51) indicate that significant between-day differences (e.g. sweat rate, sweat sensitivity, T_{sk}) would have been observed had PH and C been exposed to heat for a longer period (i.e 14 d). Mean submaximal oxygen uptake ($VO_2submax$) on day 2 was significantly lower ($p < .025$) in PH (22.48 ± 0.87 $ml \cdot kg^{-1} \cdot min^{-1}$) than in C ($26.11 \pm 0.93$ $ml \cdot kg^{-1} \cdot min^{-1}$); the corresponding mean respiratory exchange ratios were higher ($p < .025$) in PH (0.92 ± 0.02) than in C (0.84 ± 0.03). Previous reports (25,40) have observed that PH have lower $VO_2submax$ than C subjects. Mean final rating of perceived exertion (RPE) was not significantly different, between groups or between days (range: 10 - 11).

It was concluded that no substantial sodium or potassium deficit (involving electrolyte losses in sweat, urine, and feces [32]) occurred in either PH or C, as a result of daily 90 min

trials. There were no between-day or between-group differences in mean pre-exercise body weight, 24 h caloric intake, 24 h urine volume, or urine specific gravity. All mean urine specific gravity values were < 1.020 on all days, for PH and C.

There were no significant differences between PH and C in any of the following blood measurements: hematocrit, hemoglobin, mean corpuscular hemoglobin concentration, total protein, Na+, K+, osmolality. Other analyses (not shown) indicated that calcium, blood urea nitrogen, uric acid, and total bilirubin were found to be within normal ranges on all days, for PH and C. The between-day PV% were positive and large in both groups by day 5 (PH: +14.9 $\pm$ 2.9%; C: +17.1 $\pm$ 3.1%).

SERUM ENZYMES

The analysis of clinically relevant enzyme data (CPK, LDH, AST, ALT) indicated that two distinct PH groups existed. Three PH (subjects E, F, G) exhibited large CPK elevations, and were evaluated as a group (P2) separate from the other seven PH (P1), who exhibited normal serum enzyme values throughout iteration 1 of the heat acclimation process (Fig. 3). CPK was used to identify group P2 because it is an indicator of muscle injury (5) and malignant hyperthermia (24). Although Subject A was defined as heat intolerant during heat acclimation trials, he exhibited normal CPK, LDH, AST, and ALT values throughout the investigation, and was included with group P1 for enzyme data analysis. Subjects E, F and G all returned to repeat this protocol a second time (iteration 2), approximately three months

after their first testing (iteration 1); subject F returned for a third series of testing (iteration 3) because his CPK, LDH and AST levels were elevated during iteration 2. Most statistical differences between P2 and P1 (or C) occurred on day 2, during iteration 1 of this protocol (Fig.3); these rises in serum CPK (34), LDH, AST and ALT probably resulted from the 15 min step test conducted prior to day 1 (see methods).

Figure 4 presents the serum CPK, LDH, AST, and ALT levels for one member of P2 (Subject F), during iterations 1, 2, and 3 of the protocol (at 40 d, four months, and eight months after heatstroke). Although CPK, LDH, AST and ALT were elevated during the first and second iteration, they were within the normal range during the entire third iteration. This trend toward normal serum enzyme levels also was observed for subjects E and G.

SIX-HOUR HEAT TOLERANCE TESTS

Six-hour trials resulted in mean ($\pm$ SE) total sweat losses of 4.00 $\pm$ 0.31 l (HTT_{pre}) versus 4.47 $\pm$ 0.20 l (HTT_{post}) for PH, and 3.72 $\pm$ 0.41 l (HTT_{pre}) versus 3.74 $\pm$ 0.47 l (HTT_{post}) for C. There were no significant differences ($p > .05$) between groups or between days (day 1 versus day 9) in $T_{re} - T_{sk}$ gradient, T_{sk}, T_{re}, or HR. However, final T_{re} and final HR showed a decreasing trend in both PH and C (HTT_{pre} versus HTT_{post}, Fig. 5). Subject A and subject D did not exhibit this decreasing trend in T_{re} and HR, and were therefore defined as heat intolerant, based upon these six-hour heat tolerance tests.

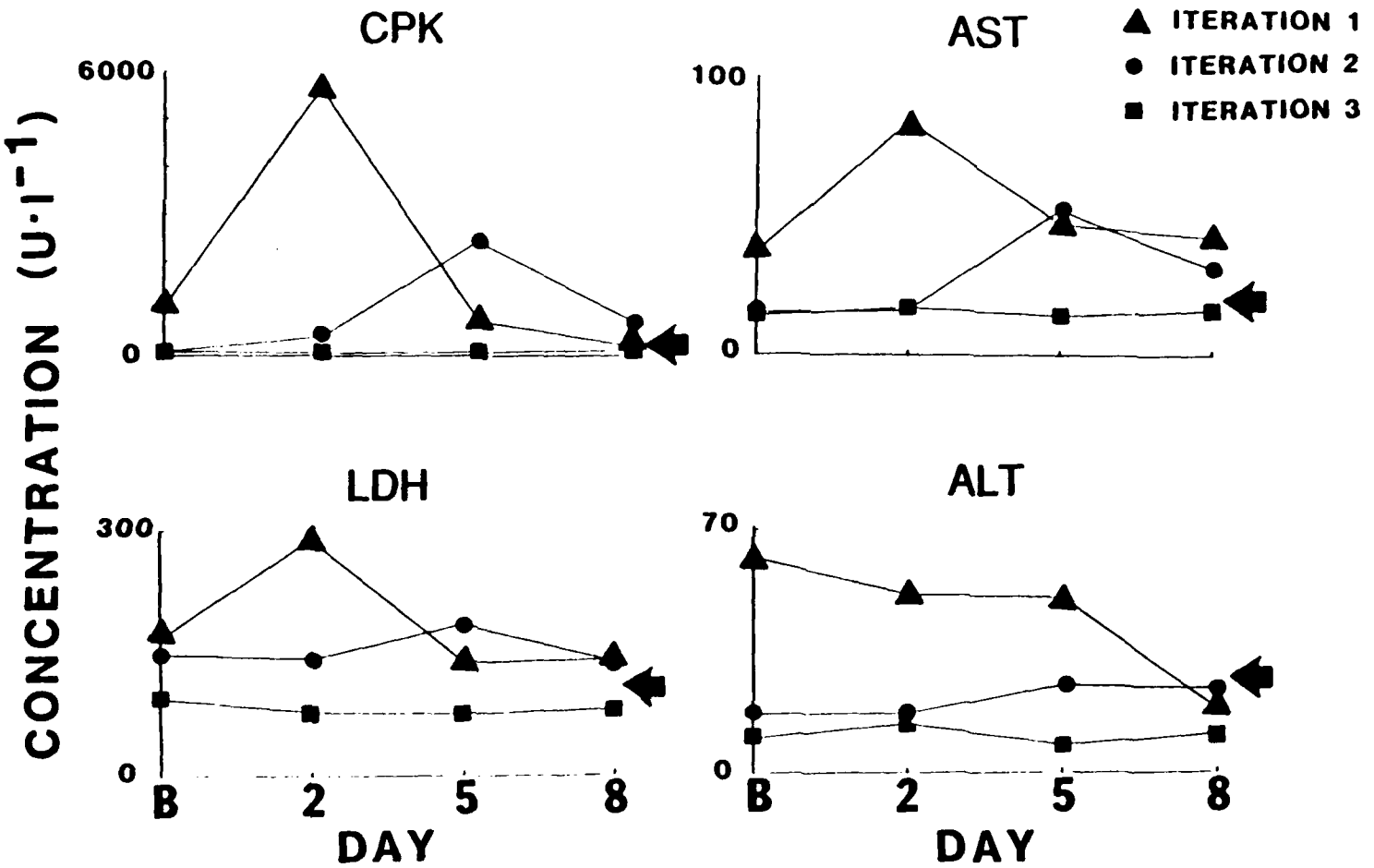

Figure 4. Pre-exercise serum CPK, LDH, AST, and ALT values of subject F, during three iterations of this protocol (40 days, 4 months, and 8 months after heatstroke, respectively). Subject F was a member of group P2 in figure 3. Arrows denote the upper level of the normal range of each enzyme.

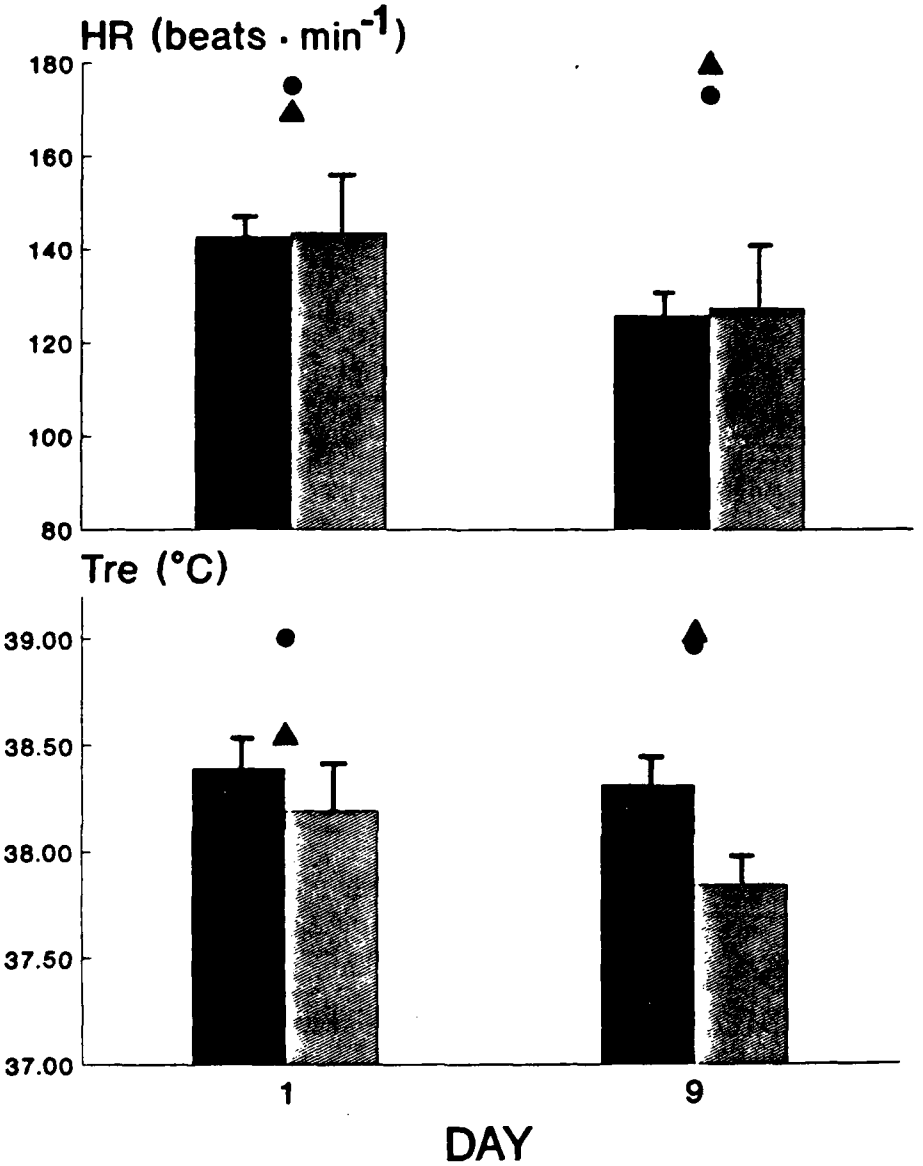

Figure 5. Mean (± SE) final HR and Tre values on day 1 (HTT_{pre}) and day 9 (HTT_{post}). Symbols are identical to those in figure 2, except that the closed triangle represents subject D. No statistically significant differences existed between days or between groups.

Discussion

The PH in the current investigation (Table 1) suffered from various degrees of heatstroke. Shibolet (42) observed in 1976 what he described as 20 "light" and 16 "severe" cases of exertional heatstroke. In the light heatstroke cases, coma was less prolonged, and hyperthermia fell rapidly within an hour; biochemical evidence of multiple system involvement was still present, however. Severe heatstroke cases, in contrast, were often moribund on admission and died early of central nervous system damage, before the multiple system disruption would have become evident (42). A major difference between light and severe heatstroke may be the length of time between collapse and the initiation of cooling therapy (5,10,18), recognizing that some cooling techniques may cool the body faster (9,39).

THE TIME COURSE OF RECOVERY

The comparison of the heat acclimation data of PH and C (Fig. 2) demonstrated that nine PH were physiologically normal. In these nine PH, the designation of "clinically normal" at the treatment facility was equivalent to "heat tolerant" in our climatic chamber, at 61 $\pm$ 7 d after exertional heatstroke (range: 25 - 99 d, see Table 1). This was not true for subject A who, in spite of normal sodium and potassium balance and clinical indices, was unable to complete 90 min trials on all days, due to a final T_{re} in excess of 39.0°C. The responses of subject A were similar to the heat intolerant prior heatstroke patients described by Shapiro (40) and Shvartz (43). Earlier it had been

reported (8) that the recovery from exertional heatstroke-induced hepatic injury in two distance runners was not complete until 11 - 12 months after heatstroke. Although this lengthy recovery time agrees well with the recovery of heat acclimation ability in subject A (at 11.5 months), this does not indicate that he had severe liver damage. In contrast, the serum indices which correlate well with the severity of liver injury (i.e. LDH, AST, ALT) (26), were elevated in subject A during hospitalization; however, these markers were below the mean for PH (Table 3), and were within the normal range, during iterations 1, 2 and 3 of this protocol.

SERUM ENZYME ELEVATIONS

Serum CPK levels indicated that three PH (subjects E, F, G) had high CPK values (838, 5625, 958 $U \cdot l^{-1}$, respectively; normal range: 33 - 213 $U \cdot l^{-1}$), and they were asked to return for additional testing. They were treated separately (as group P2) from the other seven PH (group P1) during enzyme data analysis (Fig. 3). Isoenzyme assays indicated that the CPK in the serum of P2 originated in muscle tissue (> 98 % m-m band), in all cases. These CPK elevations during exercise-heat tolerance tests are probably explained by the inactivity and detraining of P2 following heatstroke. In fact, changes in serum CPK, LDH, AST, and ALT during heat acclimation did not follow the course of serum enzyme changes after heatstroke (Table 3), suggesting a response to exercise rather than a pathological condition. It has been demonstrated (34) that similar CPK elevations occurred

following a single eccentric exercise trial.

Only one research team has previously reported the serum enzymes of prior heatstroke patients at any time greater than two weeks following exertional heatstroke (7), but their data indicated little about the time course of recovery. Figure 4 depicts the serum enzyme levels of subject F and illustrates the trend which was noted in all members of group P2. This trend involved reductions of serum CPK, LDH, AST, and ALT, from iteration 1 to iteration 2 or 3. This trend hypothetically may be explained by the restoration of normal membrane/organ function, increased physical training between successive iterations, or combinations of these factors.

HEAT ACCLIMATION AS A MEASURE OF HEAT INTOLERANCE

Senay and Kok (38) described heat intolerant miners by their inability to acclimate to repeated days of exercise in hot, humid environments. Wyndham (49) and Strydom (45) reported that two to five per cent of these recruits were innately heat intolerant. At the onset of the current investigation, it was not known whether PH were members of such a heat intolerant group, or whether situational/host factors predisposed them to heatstroke. Heat acclimation classically has been associated with reduced heart rate and decreased core temperature during a specified exercise/heat stress (17,46). Figure 2 illustrates the HR and T_{re} of PH and C, at the end of 90 min trials on days 2 and 7. Because nine PH exhibited HR and T_{re} responses that were statistically similar to those of C, hereditary heat intolerance

was excluded as a causative factor in all subjects except subject A during iteration 1. The fact that subject A ultimately acclimated to exercise in the heat, at 11.5 months after heatstroke (iteration 3), suggests: (a) he was not hereditarily, permanently heat intolerant prior to heatstroke; (b) the concept that "one heatstroke predisposes to another heatstroke" may be true temporarily, and was more likely to be true during the time that subject A was heat intolerant (25); (c) some physiological factor(s) (i.e. cardiorespiratory physical fitness) improved to allow subject A to respond normally during iteration 3.

Unlike subject A, subject E was heat tolerant (i.e. able to acclimate to heat), but experienced difficulty completing 90 min heat acclimation trials. His trials were terminated prematurely on days 2, 3, and 5 because he displayed a final T_{re} in excess of 39.0°C; this probably was related to his high M/SA, high body fat %, and low VO_2max (12,16,31,49). His T_{re} values decreased, however, from day 2 (39.0°C) to day 7 (38.4°C) of iteration 1. Also, subject E had been ordered to curtail physical training and heat exposure, and gained 9 kg of body weight, during the 82 d which elapsed between heatstroke and testing at this laboratory. Clearly, subject E possessed several characteristics (see above) which are recognized as hallmarks of increased susceptibility to hyperthermia or heat illness (12,15,36,38).

SIX-HOUR HEAT TOLERANCE TESTS

Longitudinal heat acclimation observations are essential in describing the heat tolerance of prior heatstroke patients. A

single, prolonged exercise exposure also has been defined as a heat tolerance test by some authors (45,48). Single, prolonged trials evaluate one's ability to complete a day of labor in a hot environment. The comparison of heat tolerance, defined in these two ways, is instructive and was accomplished by comparing changes in heat tolerance between days 1 and 9 (Fig. 5) with the changes in heat tolerance between days 2 and 7 (Fig. 2). When compared with Figure 2, Figure 5 indicated that subject A was unable to heat acclimate and was unable to successfully complete HTT_{pre} and HTT_{post}. However, despite manifesting normal heat acclimation responses, subject D exhibited a poorer response on HTT_{post} than HTT_{pre}, and was defined as heat intolerant. To our knowledge, no previous investigation has demonstrated such a discrepancy between types of heat tolerance tests. This may indicate that these two methods of determining heat tolerance (90 min versus 6 h trials) measure different aspects of heat tolerance (e.g. underlying physiological adjustments and functional states of organ systems associated with various fitness, training, and heat acclimation levels [4]). If a single heat tolerance test is utililized, it should involve exercise of at least two hours in duration (49).

PREDISPOSING FACTORS

Because of the many factors that may predispose an individual to heatstroke (5,6,10,14,27,38,42,45), it is difficult to establish a pattern of factors which are common to members of PH. However, interviews (Table 4) have confirmed that several of

these factors may have been present. For example, subject B had not successfully completed previous training runs, during the three days prior to heatstroke; he stopped because of weakness and dizziness, which he attributed to a low-grade infection that had been diagnosed five weeks prior to collapse. Subjects E, I and J acknowledged that they experienced asthma, hay fever, or an upper respiratory infection prior to heatstroke; impaired respiration and medications may have altered their metabolic responses during exercise. Richards et al. (35) previously reported a high incidence of upper respiratory infection (n = 17) among 56 cases of heat exhaustion at a mass participation road race.

The Predisposing Factors Questionnaire (Table 4) indicated that sleep loss and generalized fatigue were the most common factors acknowledged by PH, during the five days prior to heatstroke. This was due either to the training or duty which PH had undertaken. Table 2 illustrates that six PH (subjects E-J) had recently begun (4 - 10 d) specialized training which involved a sudden increase in physical training, accumulated fatigue, reduced sleep (e.g. 3 - 4 h per night), and psychological stress. Khogali (28) described a series of stressful events (e.g. lack of sleep, overcrowding, noise) encountered by two million religious pilgrims which led to a relatively high incidence of heatstroke (2.3 per 1000). In one PH (subject F), transcontinental flight preceded the beginning of specialized training, and desynchronization of circadian rhythms

may have been involved (47). Subject D had slept less than four hours during the night prior to experiencing heatstroke, because he had performed night duty. Sleep deprivation apparently has little effect on physical performance (19), but has been shown to reduce the thermosensitivity of sweating and peripheral blood flow (29), to reduce high-energy phosphate formation and serum ATP levels (33), and to double energy expenditure in animals (37). Future investigations of these effects may clarify the mechanism by which sleep loss acts as a predisposing factor to heatstroke (28,42).

It is also possible that substrate depletion may be a predisposing factor. Six PH (subjects D through I) acknowledged generalized fatigue during the five days prior to heatstroke (Table 4); five of these men experienced a dramatic increase in the amount of physical training, as they participated in specialized, high-stress training. Under these conditions, it is likely that all PH experienced markedly reduced muscle glycogen stores, because this can occur in as little as 2 - 4 h (41). Both muscle glycogen depletion (27) and hypoglycemia (10) have been proposed as factors which may predispose humans to heatstroke. Cellular energy depletion and increased reliance on anaerobic energy metabolism also have been identified as primary theoretical factors in heatstroke pathophysiology (20,21,23). It is interesting to note that PH relied on carbohydrate metabolism (e.g. higher respiratory exchange ratio) to a significantly greater degree ($p < .025$) than C.

Lavenne and colleagues studied the heat tolerance of 50 Belgian mine workers in 1966 (31), concluding that a VO_2max of 40 $ml \cdot kg^{-1} \cdot min^{-1}$ may be considered to be the boundary between "those who are able to tolerate high temperatures and those who are adversely affected." Shvartz (43) and Epstein (16) also reported low VO_2max values (41.2 and 40.0 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively) for heat intolerant prior heatstroke patients, when compared to C. In close agreement with these findings, the three lowest VO_2max values ($ml \cdot kg^{-1} \cdot min^{-1}$) in the current investigation were recorded for subject A (43.74), subject E (45.73), and subject D (38.37). Interestingly, subject A was heat intolerant (iterations 1 and 2); subject E had three of his heat acclimation trials terminated (days 2, 3, and 5) because of T_{re} in excess of 39.0°F; and subject D exhibited elevated final HR and final T_{re} values during a six-hour trial (results not shown, see methods). Eighty percent of PH were running in a group at the time of heatstroke (Table 2). Those PH who had low VO_2max values probably experienced above average rectal temperatures, because they were running at higher relative exercise intensities than other group members (49). Obviously, if these individuals had been running in a competitive footrace (as subjects C and J were), then development of hyperthermia would have been even more likely.

Virtually all scientific and clinical reports of exertional heatstroke involve males. For example, the 10 PH in this investigation, as well as every prior heatstroke patients described in the case reports and laboratory investigations

above, were males. The following hypotheses may be involved: (1) scientific research has historically utilized male test subjects, (2) males are placed in situations which result in heatstroke, and are likely to push themselves to the point of collapse, and (3) males are predisposed to heatstroke because of inherent hormonal, physiological or morphological differences. Although Kumar et al. (30) reported that the incidence of non-exertional heatstroke among males was three times that of females, and attributed this to an unexplained greater susceptibility in males, gender effects deserve future research consideration.

Conclusions

1. A determination of "clinically normal" at the treatment facility was not always equivalent to being physiologically "heat tolerant". The rate of recovery from exertional heatstroke was unique to each case. At 61 $\pm$ 7 d following heatstroke, nine out of 10 PH exhibited normal heat acclimation, thermoregulation, whole body sodium and potassium balance, sweat gland function, and clinical values. Only subject A was defined heat intolerant (at approximately two and seven months after heatstroke), but was defined heat tolerant at 11.5 months.

2. Subject A demonstrated that complete recovery from exertional heatstroke may require 11.5 months.

3. Exertional heatstroke occurred in most PH while they were running in a group, at moderate exercise intensity, between 0600h - 1000h. Environmental temperature was not harsh (19 -

28°C db), but relative humidity was high (> 66 %rh).

4. The lowest VO_2max values (range: 38.37 - 45.73 $ml \cdot kg^{-1} \cdot min^{-1}$) were observed among the three PH who performed poorly, at some point, in exercise-heat exposures.

5. Although these elevations in CPK (group P2) may have been sequelae of heatstroke (i.e. abnormal membrane permeability), the rate of CPK rise and fall supports the hypothesis that they were due to the eccentric nature of one exercise trial (34) and the lack of physical training. Subsequent iterations of this protocol revealed a trend toward normal serum CPK levels in these three PH.

6. None of the 10 PH in this investigation were hereditarily heat intolerant, based upon their ability to acclimate to heat. Multiple stressors (e.g. sleep loss, sudden increase in physical training, lengthy exposure to heat stress) may be critical in inducing heat injury.

7. Heat intolerance (e.g. an inability to adapt to 90 min of recuurent exercise in a hot environment) occurs in a small percentage of prior heatstroke patients, and occurred temporarily in subject A.

8. Of the factors measured in the hospital or in the laboratory, none was clearly related to prognosis, recovery from heatstroke, or performance during heat acclimation trials. Previously described prognostic factors (e.g. AST > 1000 $U \cdot l^{-1}$, coma duration > 2 h) (42) were not predictive of the ability of PH to work in the heat.

9. The results of the current investigation indicate that clinically normal PH, during recovery, can benefit from well-planned physical training and heat acclimation programs which include on-site medical monitoring, gradual increments in the duration and intensity of heat exposure (e.g. core body temperature increase expressed in terms of degree-minutes [22,23]), and gradual increments in exercise frequency/duration/intensity.

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